



US00RE43797E

(19) **United States**
 (12) **Reissued Patent**
 Oppenheimer et al.

(10) **Patent Number:** US RE43,797 E
 (45) **Date of Reissued Patent:** *Nov. 6, 2012

(54) **METHODS OF ADMINISTERING TETRAHYDROBIOPTERIN**

(75) Inventors: **Daniel L. Oppenheimer**, Castro Valley, CA (US); **Alejandro Dorenbaum**, Mill Valley, CA (US); **Augustus O. Okhamafe**, Concord, CA (US)

(73) Assignee: **Biomarin Pharmaceutical Inc.**, Novato, CA (US)

(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/299,499**

(22) Filed: **Nov. 18, 2011**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **7,947,681**
 Issued: **May 24, 2011**
 Appl. No.: **12/577,509**
 Filed: **Oct. 12, 2009**

U.S. Applications:

- (63) Continuation of application No. 12/329,838, filed on Dec. 8, 2008, now Pat. No. 7,612,073, which is a continuation of application No. PCT/US2008/060041, filed on Apr. 11, 2008.
 (60) Provisional application No. 60/922,821, filed on Apr. 11, 2007, provisional application No. 61/019,753, filed on Jan. 8, 2008.

(51) **Int. Cl.**

A01N 43/58 (2006.01)
A61K 31/50 (2006.01)
A01N 43/60 (2006.01)
A61K 31/495 (2006.01)

(52) **U.S. Cl.** **514/249**(58) **Field of Classification Search** 514/249
 See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

4,550,109 A	10/1985	Folkers et al.
4,778,794 A	10/1988	Naruse et al.
5,753,656 A	5/1998	Sakai et al.
6,288,067 B1	9/2001	Okamura et al.
6,410,535 B1	6/2002	Kashiwagi et al.
6,544,994 B2	4/2003	Rabelink et al.
6,995,158 B2	2/2006	Rabelink et al.
7,566,462 B2	7/2009	Jungles et al.
7,566,714 B2	7/2009	Oppenheimer et al.
7,727,987 B2	6/2010	Moser et al.
2006/0035900 A1	2/2006	Moser et al.
2006/0194808 A1	8/2006	Richardson et al.
2006/0211701 A1	9/2006	Muntau-Heger et al.
2008/0075666 A1	3/2008	Dudley et al.
2008/0146577 A1	6/2008	Matalon et al.
2008/0213239 A1	9/2008	Morris

FOREIGN PATENT DOCUMENTS

EP	1964566	12/2005
EP	1757293	2/2007
WO	WO 2004/058268	7/2004
WO	WO 2005/049000	6/2005

OTHER PUBLICATIONS

Belanger-Quintana, et al., Spanish BH4-responsive phenylalanine hydroxylase-deficient patients: Evolution of seven patients on long-term treatment with tetrahydrobiopterin, *Mol. Gen. Metab.*, 86:S61-S66 (2005).

Blau, et al., Optimizing the use of sapropterin (BH4) in the management of phenylketonuria, *Mol. Gen. Metab.*, (2009), doi:10.1016/j.ymgme.2009.01.002.

Calbet, et al., Role of caloric content on gastric emptying in humans, *J Physiol.*, 498.2: 553-559 (1997).

Feige, et al., Plasma tetrahydrobiopterin and its pharmacokinetic following oral administration, *Mol. Gen. Metab.*, 81:45-51 (2004).

Fleisher et al., Drug, Meal and Formulation Interactions Influencing Drug Absorption After Oral Administration, *Clin. Pharmacokinet.*, 37(3):233 (1999).

Gu et al., Predicting Effect of Food on Extent of Drug Absorption Based on Physicochemical Properties, *Pharmaceutical Research*, 24(6):1118 (2007).

Hennermann, et al., Long-term treatment with tetrahydrobiopterin increases phenylalanine tolerance in children with severe phenotype of phenylketonuria, *Mol. Gen. Metab.*, 86:S86-S90 (2005).

Kuvan™ [sapropterin dihydrochloride(BH4)] Tablets Product Information, pp. 1-17 (Dec. 2007).

Levy, et al., Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study, *The Lancet*, 370:504-510 (2007).

Levy, et al., Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment, *Mol. Gen. Metab.*, 92:287-291 (2007).

Musson et al., The bioavailability of Kuvan™ (sapropterin dihydrochloride) from intact or dissolved tablets administered with or without food to healthy volunteers, Abstract 70, published on p. 259 of *Molecular Genetics and Metabolism*, vol. 93, pp. 221-268 (2008) (presented at The Society for Inherited Metabolic Disorders (SIMD) Annual Meeting, Mar. 2-5, 2008, Pacific Grove, California). O'Brien and Haddard, *US Pharmacist*, 22:6: 62 (1997).

Ponzone, et al., Hyperphenylalaninemia and pterin metabolism in serum and erythrocytes, *Clinica Chim. Acta.*, 216:63-71 (1993).

Schaub et al., Archives of Disease in Childhood, vol. 53, pp. 674-683 (1978).

Schirck's Laboratories, Summary of Product Characteristics—Tetrahydrobiopterin 10 mg/50 mg Tablets, dated Jan. 7, 2004.

Schmidt, et al., Single dose oral tetrahydrobiopterin (BH4) leads to a prolonged increase in aortic BH4 levels in ApoE-KO mice, *Abstracts/Atherosclerosis*, 193:S1-S5 (2007).

Shintaku, et al., Long-Term Treatment and Diagnosis of Tetrahydrobiopterin-Responsive Hyperphenylalaninemia with a Mutant Phenylalanine Hydroxylase Gene, *Ped. Res.*, 55(3):425-430 (2004).

(Continued)

Primary Examiner — Yong Chong

(74) *Attorney, Agent, or Firm* — Marshall, Gerstein & Borun LLP

(57) **ABSTRACT**

The present invention is directed to treatment methods of administering tetrahydrobiopterin, including in oral dosage forms, in intravenous formulations, and with food. Also disclosed herein are biopterin assays for measuring the amount of biopterin and metabolites of biopterin in a sample.